

REMARKS:

In the Office Action dated January 22, 2007, claims 1-14, in the above-identified U.S. patent application were rejected. Reconsideration of the rejections is respectfully requested in view of the above amendments and the following remarks. Claims 1-14 remain in this application.

Claims 1-7 and 12-14 were rejected under 35 USC §103(a) as unpatentable over Neidhardt (WO 93/16099) in view of Ron (U.S. Patent No. 5,171,579) and Avis.

The Avis reference provides a general discussion of lyophilization but has nothing to do with proteins in particular. Many substances are indicated as being possible agents to make the dried-product plug occupy essentially the same volume as that of the original solution. The disclosure of Avis would not have guided one skilled in the art to select mannitol for use with MP52 from the numerous recited substances. As discussed in prior responses, applicants have found that products used in the prior art were not successful when used with MP52 and thus the use of specific substances is not predictable from the general disclosure in the cited prior art.

Ron does not cure the deficiencies in Avis as Ron does not suggest that mannitol is suitable for the use in a lyophilized product of MP52 either. Ron generally suggests that additional optional components such as cryogenic protectors might be useful. However, no examples were carried out in order to show that mannitol is in fact suitable in the connection with osteogenic proteins. Mannitol tends to form crystals during freezing and to leave the protein exposed (Williams NA, Lee Y, Polli GP, et al., "The Effects of Cooling Rate on Solid Phase Transitions and Associated Vial Breakage Occurring in Frozen Mannitol Solutions," J Parent Sci Tech, 40:135-141, 1986). Mannitol has also been found to provide little biological protection during freezing since

it crystallizes and is thereby removed from the preparation (Gerald D. J. Adams, J. Richard Ramsay, Optimizing the lyophilization cycle and the consequences of collapse on the pharmaceutical acceptability of *erwinia*L-Asparaginase, <http://www3.interscience.wiley.com/cgi-bin/abstract/72505070/ABSTRACT>). The suggestion of mannitol as a possible cryogenic protector does not show that mannitol is in fact successful and it was unpredictable from Ron whether or not the use of mannitol would be helpful in context with a lyophilized MP52 product. Though MP52 and BMP-2 belong to the same protein family, as previously pointed out, they do not exhibit identical physical behavior. Properties such as solubility cannot be transferred from one protein to another since individual amino acids on the protein surface have different hydrophobicity and can also show different solution behavior and different tendencies to aggregation. In general, it is not possible to transfer data from one protein to another even if they are in the same family. Thus, even if Ron had shown that mannitol acts as a cryogenic protector of BMP-2, which he did not, one would not assume that mannitol could also be used with MP-52. Since not all cryoprotectants can be used with all proteins, applicants contend that one skilled in the art would not reasonably expect mannitol to be useful with MP52 without testing. In view of the above discussion, applicants request that this rejection be withdrawn.

Claims 7-14 were rejected under 35 USC §103(a) as unpatentable over Neidhardt in view of Ron and Avis further in view of Chang. As discussed in applicant's prior response, Chang does not cure the deficiencies in Neidhardt, Ron and Avis as Chang also shows that no general predictions can be made about the lyophilization conditions for specific proteins. Chang, on page 1325, first column, discloses that

"despite the numerous freeze-thawing studies on proteins, the choice of these solutes and development of stable formulations is still largely empirical because of the lack of a full understanding of the relative importance of the various stresses arising during freezing and of mechanisms by which additives protect proteins against these stresses". In other words, for every protein, optimum conditions must be determined individually and cannot be predicted from the results obtained with other proteins. In view of the above discussion, applicants request that this rejection be withdrawn.

Applicants point out that the argumentation in applicant's prior response regarding mixing ratios included a clerical error. Applicants remarks stated that "22 mg of BMP-2 and 8 mg of mannitol were used, i.e. a mixing ratio of 1:364". This should have stated "22 µg of BMP-2". In any case, a skilled artisan would have assumed that BMPs are used with considerably higher dosages of mannitol than is the case according to the present invention with MP52 wherein the optimum mixing ratio from 1:5-50 is sufficient.

Claims 7-10 and 12-14 were rejected under 35 USC §103(a) as unpatentable over Neidhardt, Ron and Avis in view of Chang, further in view of Hansen, in light of the MeSH definition of "poloxamer". As discussed above, the combination of Neidhardt, Ron, Avis and Chang, does not suggest that mannitol should be used when lyophilizing MP52. Hansen is cited only for the disclosure of surfactants for stabilization of freeze-dried proteins and does not cure the deficiencies in Neidhardt, Ron, Avis and Chang regarding the use of mannitol with MP52 in a lyophilized composition. In view of the above discussion, applicants request that this rejection be withdrawn.

Claim 10 was rejected under 35 USC §112, second paragraph, as indefinite.

The term "substance" has been deleted from claim 10. In view of this amendment applicants request that this rejection be withdrawn.

Applicants respectfully submit that all of claims 1-14 are now in condition for allowance. If it is believed that the application is not in condition for allowance, it is respectfully requested that the undersigned attorney be contacted at the telephone number below.

In the event this paper is not considered to be timely filed, the Applicant respectfully petitions for an appropriate extension of time. Any fee for such an extension together with any additional fees that may be due with respect to this paper, may be charged to Counsel's Deposit Account No. 02-2135.

Respectfully submitted,

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